

# Management of Anticoagulation in the Hospitalized Patient

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# Two Major Categories in the Hospitalized Patient

- ▶ The surgical patient elective versus emergent cases
- ▶ Is bridging necessary
- ▶ How do I shift treatment based on the surgical procedure considered: low risk for bleeding versus high risk for bleeding
- ▶ What is the risk of thrombosis in this patient
- ▶ Is the anticoagulant being used easily reversible
- ▶ When do I restart anticoagulation, what is safe
- ▶ What are risks and benefits
- ▶ What comorbid conditions need to be considered

# Stratify risk factors for perioperative TE

JAFFER A K Cleveland Clinic Journal of Medicine  
2009;76:S37-S44

**TABLE 1**  
ACCP's suggested risk stratification for perioperative thromboembolism\*

Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
<b>High</b> (>10%/yr risk of ATE or >10%/mo risk of VTE)	Any mechanical mitral valve Older aortic valve Recent (< 6 mo) stroke or TIA	CHADS <sub>2</sub> score of 5 or 6 Recent (< 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 mo) VTE Severe thrombophilia
<b>Moderate</b> (4%–10%/yr risk of ATE or 4%–10%/mo risk of VTE)	Bileaflet aortic valve and one of the following: atrial fibrillation, prior stroke/TIA, hypertension, diabetes, heart failure, age > 75 yr	CHADS <sub>2</sub> score of 3 or 4	VTE within past 3–12 mo Recurrent VTE Nonsevere thrombophilic conditions Active cancer
<b>Low</b> (<4%/yr risk of ATE or <2%/mo risk of VTE)	Bileaflet aortic valve without atrial fibrillation and no other risk factors for stroke	CHADS <sub>2</sub> score of 0–2 (and no prior stroke or TIA)	Single VTE within past 12 mo and no other risk factors

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ACCP = American College of Chest Physicians; ATE = arterial thromboembolism; VTE = venous thromboembolism; TIA = transient ischemic attack

Low risk → Stop anticoagulant but not start bridging anticoagulant

# BRIDGE Trial

Heparin

Placebo



# The Bridge Trial

*We still have unanswered questions.....*The BRIDGE trial

- The fundamental question of whether bridging anticoagulation is necessary during perioperative warfarin interruption has remained unanswered
- The BRIDGE trial was designed to address a simple question:  
***in patients with atrial fibrillation, is heparin bridging needed during interruption of warfarin therapy before and after an operation or other invasive procedure?***
- The authors hypothesized that forgoing bridging altogether would be noninferior to bridging with low-molecular-weight heparin for the prevention of perioperative arterial thromboembolism and would be superior to bridging with regard to the outcome of major bleeding.





# Study Outcomes

## BRIDGE: Results (safety)

- The primary safety end point didn't differ significantly between the two groups (p=0.763)
- There was a numerical increase in minor bleeding complications (about 18% vs 10%) among cangrelor recipients

### Excessive CABG-related bleeding (during the procedure or after until discharge)

End point*	Cangrelor, n=106 (%)	Placebo, n=101 (%)	OR (95% CI)
Total CABG-related bleeding	11.8	10.4	1.15 (0.47–2.79)
Surgical reexploration	2.0	2.1	0.94 (0.13–6.81)
24-hour chest-tube output >1.5L	7.8	5.2	1.55 (0.49–4.91)
Incidence of packed RBCs >4 U	5.9	8.3	0.69 (0.23–2.06)

\*Defined as occurrence of one or more of the following events during CABG or the postoperative hospitalization: Surgical reexploration, 24-hour chest-tube output >1.5 L, packed RBC transfusion >4 units)

# Outcomes

**Table 3. Study Outcomes.**

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	<i>number of patients (percent)</i>		
<b>Primary</b>			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
<b>Secondary</b>			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

\* P value for noninferiority.

† P value for superiority.

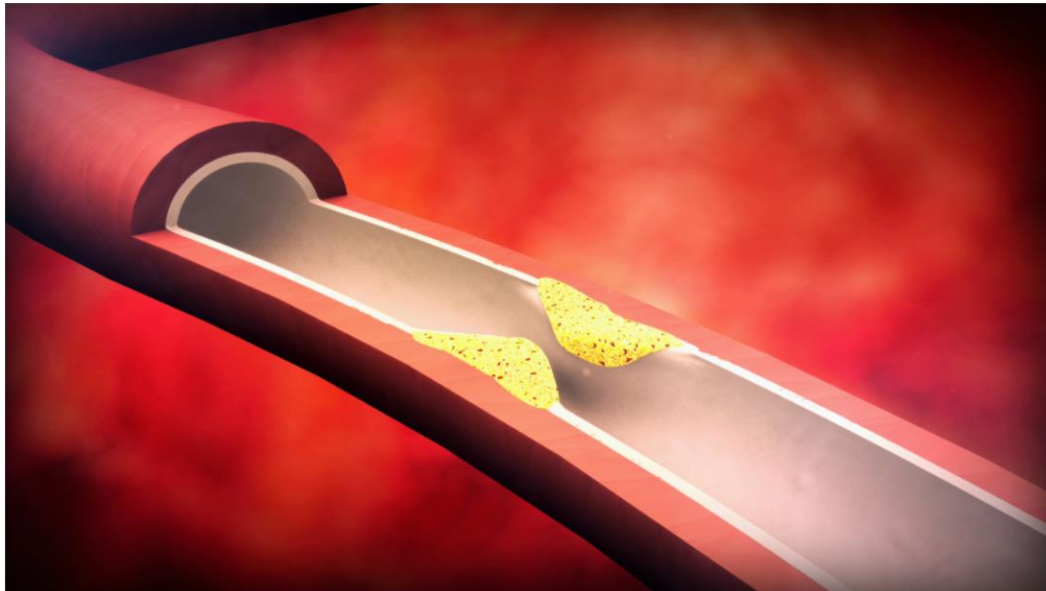
# Two Major Categories-continued

- ▶ The medical patient admitted on oral anticoagulants
- ▶ What are the risk factors-high, medium, low for thrombosis
- ▶ What is the CHAD scoring
- ▶ Do I consider the effects of antibiotics and if there is a component of
- ▶ Malabsorption such as due to diarrhea or prior intestinal bypass surgeries
- ▶ Does the renal function affect the timing of anticoagulants if there is associated hemorrhage
- ▶ Do I shift management if bleeding is life threatening versus moderately severe



# Review

- ▶ Clotting and lysing is a dynamic continuous process, responding to the effects of illness, trauma, end-organ damage, and medications.
- ▶ Prior to 1992 it was felt that the coagulation cascade simply involved intrinsic components, extrinsic components, and a common pathway.
- ▶ Today the coagulation scheme of clotting and lysis involves three major categories of activity-the vascular system, the platelet functioning component, and the procoagulant factors all interacting in a dynamic fashion



# Vascular Phase

- ▶ Smooth muscles in arterioles and arteries induce vasoconstriction and tissue factor release
- ▶ Exposed basement membranes bind VWF and platelets
- ▶ Endothelial cells can secrete prostacyclin (platelet inhibitor) nitric oxide (a relaxing factor), heparan sulfate, tissue factor pathway inhibitor, and a protein C regulatory system.
- ▶ Damaged or activated endothelial cells through trauma or inflammation induces tissue factor release and secretes von Willebrand factor

# Platelet Phase

- ▶ Adhesion is the first response that seals the endothelial gaps—this is the mechanism behind the petechiae seen with bleeding associated with defective or quantitative defects of platelets-not enough or sufficient to control seeping of RBC's through vessel wall
- ▶ Aggregation of platelets into “plug” occurs as platelet becomes activated and begins to release contents-this process requires fibrinogen
- ▶ Secretion is the discharge of the contents of the platelet granules to strengthen the platelet plug in response to the trauma or inflammation

# Procoagulant Phase

- ▶ There are 16 procoagulants ranging in half-life from 6 hours (factor VII) to 156 hours (Fitzgerald factor)
- ▶ The Vitamin K dependent prothrombin group includes prothrombin, Factor VII, IX, and X, and the regulatory proteins C and S
- ▶ Previously it had been considered that the first phase was intrinsic pathway, followed by extrinsic, then common pathway for clotting to occur
- ▶ Currently the system is viewed as dynamic and multifaceted with continual physiologic balances of clotting and lysis
- ▶ Traditional clotting studies only require about 35% factor activity to be normal so minor abnormalities can be easily missed with screening tests

# Three Presurgical cases admitted: what do you do?

- ▶ A. 75 yo male Afib CHADS 2=4 (HTN, CHF, DM) on warfarin hip fracture repair- is he a candidate for bridging therapy, when should warfarin be resumed?
- ▶ B. 48 yo female on warfarin with history of recurrent VTE last episode 2010, scheduled for cholecystectomy laparoscopically
- ▶ C. 65 yo male on warfarin due to mechanical mitral valve post colonic resection for diverticular disease.
- ▶ What is bridging therapy?

# Ask these questions

- ▶ Do I need to stop anticoagulation
- ▶ How many days prior to a procedure is sufficient
- ▶ Should the patient be bridged



## Original CHADS<sub>2</sub> Score

<b>C</b>	Congestive Heart Failure	<b>1</b>
<b>H</b>	Hypertension (>140/90mmHg)	<b>1</b>
<b>A</b>	Age <u>&gt;</u> 75	<b>1</b>
<b>D</b>	Diabetes Mellitus	<b>1</b>
<b>S<sub>2</sub></b>	Prior TIA or stroke	<b>2</b>

# ACCF/AHA/ESC 2006 Guidelines and 2011 Focused Update

Risk Category	Recommended Therapy
No risk factors	<ul style="list-style-type: none"> <li>Aspirin (81-325 mg daily) or no therapy</li> </ul>
1 moderate risk factor	<ul style="list-style-type: none"> <li>Aspirin (81-325 mg daily) or warfarin</li> <li>Alternative dabigatran (nonvalvular AF)*<sup>2</sup></li> </ul>
Any high risk factor or >1 moderate risk factor	<ul style="list-style-type: none"> <li>Warfarin</li> <li>Alternative dabigatran (nonvalvular AF)*<sup>2</sup></li> </ul>

The European guidelines recommend anticoagulation over aspirin for most patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥1 for nonvalvular AFib<sup>13</sup>

#### Less validated/ weaker risk factors<sup>1</sup>

- Female sex
- Age 65 to 74 years
- Coronary artery disease
- Thyrotoxicosis

#### Moderate-risk factors<sup>1</sup>

- Age ≥75 years
- Hypertension
- Heart failure
- LVEF ≤35%
- Diabetes mellitus

#### High-risk factors<sup>1</sup>

- Previous stroke, TIA, or embolism
- Mitral stenosis
- Prosthetic heart valve\*

**Abbreviations:** ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ESC = European Society of Cardiology; HRS = Heart Rhythm Society; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

\*Dabigatran is an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function).

(For references, see text.)

# Risk factors for A.F.

- ▶ High: CHADS score 5-6
  - ▶ recent CVA or TIA
  - ▶ rheumatic heart disease
- ▶ Moderate: CHADS score 3-4
- ▶ Low: CHADS score 0-2

# Risk Factors for VTE

- ▶ High: recent VTE (within 3 months)
- ▶ severe thrombophilia such as deficiency of Protein C or S or antithrombin, antiphospholipid antibody
- ▶ Moderate: VTE in past 3-12 months
- ▶ Low: VTE more than 12 months non severe thrombophilia, no other risk factors heterozygous Factor V Leiden, recurrent VTE, or active cancer

# Risk Factors with Mechanical heart valves

- ▶ High: any mitral valve prosthesis
- ▶ recent CVA or TIA
- ▶ Moderate: bileaflet aortic valve prosthesis and one or more risk factors:
  - ▶ AF, prior CVA or TIA, HTN, DM, CHF, age greater than 75
- ▶ Low: bileaflet AV with no other risk factors

# Why not just bridge every patient on oral anticoagulants?

- ▶ Bridging is associated with a 3 fold increase in risk of bleeding and no decrease in thrombosis with fatal outcome
- ▶ THE BRIDGE TRIAL-Siegel, D., Circulation 2012



# So, do we bridge or not?

- ▶ Standard of Care guidelines recommend bridging in high risk patients despite risk of bleeding
- ▶ Do not bridge VTE unless event was recent (within 3 months)
- ▶ Recurrent VTE on anticoagulants
- ▶ Very high risk thrombophilia
- ▶ Active cancer considered to be terminal within 6 months and increased risk of thrombosis

# Case 1

- ▶ 75 yo male Afib CHADS2=4 (HTN, CHF, DM) on warfarin for hip fracture repair
- ▶ This patient is considered a moderate risk for thrombosis with the surgical procedure considered high risk for bleeding
- ▶ Do not bridge

## Case 2

- ▶ 48 yo female with history of VTE recurrent last episode 2010 on warfarin
- ▶ Currently scheduled for laparoscopic cholecystectomy
- ▶ This case is considered low risk for VTE and potentially high risk for bleeding from surgery if open laparotomy becomes necessary
- ▶ Do not bridge this patient
- ▶ Use usual antithrombotic precautions
- ▶ Remember there is no evidence to support just compression devices

# Case 3

- ▶ 65 yo male on warfarin due to mechanical mitral valve post colonic resection
- ▶ This case is considered high risk for thrombosis and high risk for post op bleeding due to bridging.
- ▶ Use caution and proceed

# What is timing for stopping anticoagulants

- ▶ If risk of bleeding is low such as colonoscopy then hold AC for 2-3 half lives keeping in mind if there is associated renal insufficiency there will be additional delays in drug clearance
- ▶ If risk of bleeding is high such as hip fracture or thoracic surgery then hold anticoagulants for 4-5 times the half life of the drug
- ▶ Always consider renal function in determining timing of holding meds and additional comorbid conditions that may aggravate bleeding and/or thrombosis

# Post Op factors for DOAC's

- ▶ Rapid onset of action timing depends on surgery consider step up approach and remember that it is safest to restart 48-72h post procedure to avoid hemorrhage from the surgical site
- ▶ Remember timing of warfarin since effective anticoagulation takes 5-10days
- ▶ Could you easily reverse the anticoagulant effects if bleeding did occur



# Management of Medical Conditions in acute setting

68 yo female with AF on warfarin admitted with UGI bleed INR 3.5. Received 2u RBC's, vitamin K, FFP. Urgent endoscopy revealed gastric ulcer, PPI started

When do you restart anticoagulation?

Never

One month

Refer to PCP at discharge

# Ref: Witt et al, Arch of Int Med 2012

- ▶ Review of GI bleeds and anticoagulation
  - ▶ No thrombosis if resumption of therapy began within 14 days
  - ▶ Highest risk of GI bleed recurrent was within 1-7 days of bleed
  - ▶ Must restart to decrease risk of death
- 
- ▶ Additional ref: Querschi, A. J. Cardio 2013

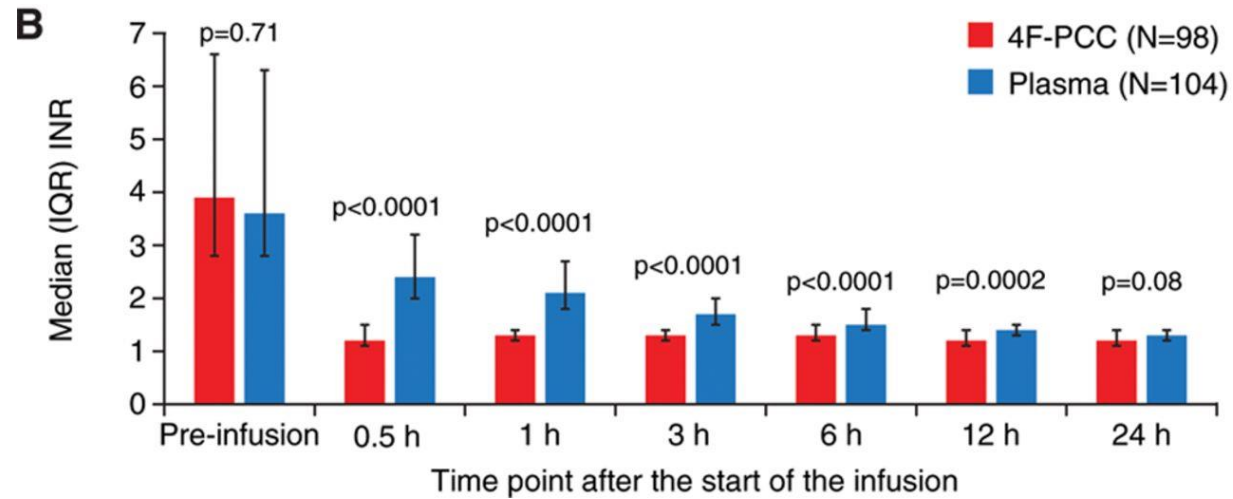
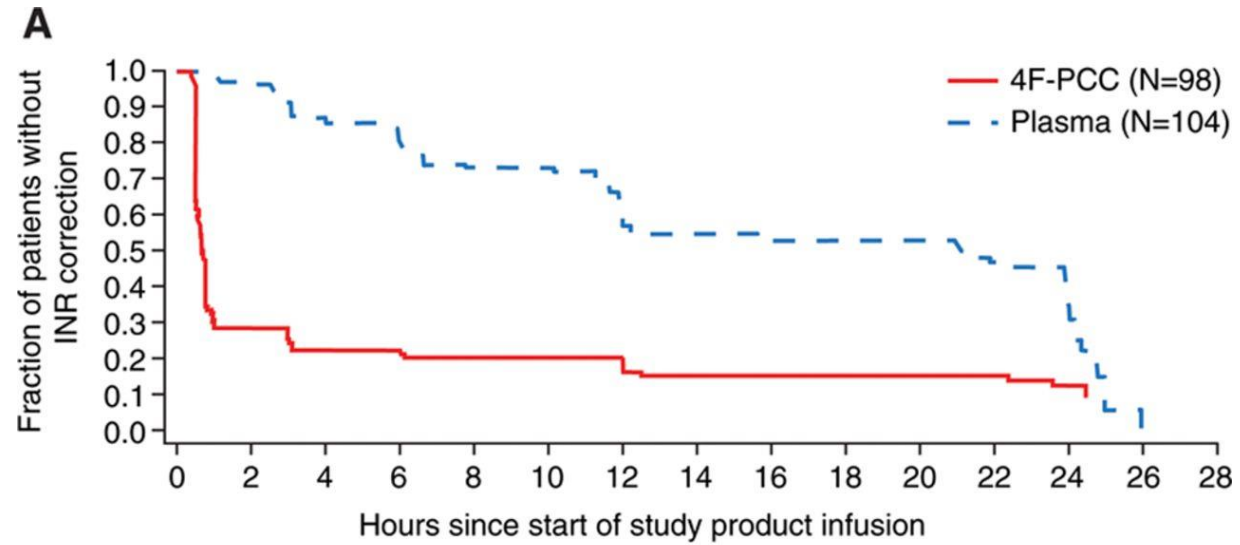
# Therefore....

- ▶ Case of GI bleed can safely be restarted 7-14 days post bleed and stabilization
- ▶ Always consider risk/benefit of timing of anticoagulants

- ▶ You are on duty in the ER and a 56 yo asthenic caucasian female presents with her family relating she is acting “funny” and they are worried she is having a stroke. She has a history of coronary stents placed 3 years ago and has been on Eliquis.
- ▶ Urgent CT of brain revealed thalamic hemorrhage with no associated cerebral edema or shift
- ▶ Do you hold next dose of Eliquis or DC
- ▶ Transfuse with FFP? Or use PCC ?

# Acute Life threatening bleed

- ▶ Consider ac being used and if it is reversible.
- ▶ What is the half life of the drug and when was the last dose taken
- ▶ If you reverse the drug how long will it take
- ▶ If it is life threatening consider
- ▶ Cofact 25u/kg or Feiba 50ie/kg or novoseven (rFVIIa)90ug/kg
  
- ▶ Moderate risk—supportive care

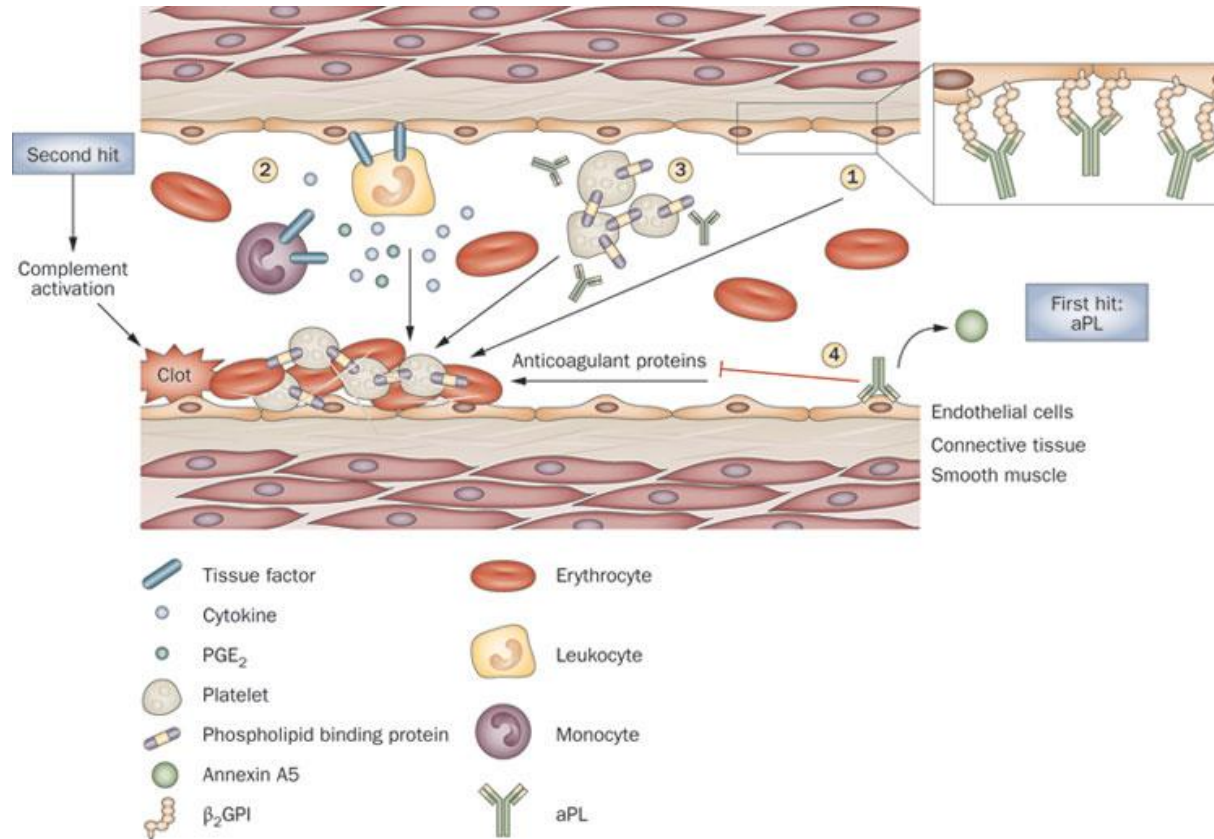




# Evidence to consider reversal

- ▶ Not using reversal agent is standard of practice although
- ▶ Faced with life threatening hemorrhage
- ▶ Giving PCC reduces clot initiation time and corrects thrombin generation
- ▶ Consider availability—how long will it take to get and will the half life of the ac leave no further room for correction.

# Antiphospholipid Syndrome



Pathogenesis of antiphospholipid syndrome Understanding the antibodies (PDF Download Available).  
 Available from  
[https://www.researchgate.net/publication/51111206\\_Pathogenesis\\_of\\_antiphospholipid\\_syndrome\\_Understanding\\_](https://www.researchgate.net/publication/51111206_Pathogenesis_of_antiphospholipid_syndrome_Understanding_)

# Thrombophilia Types

- ▶ Inherited thrombophilias have increased or decreased procoagulant activity such as Factor V Leiden or Protein C or S deficiency (less common) with an incidence of .4% to 5% in the general population .
- ▶ Acquired lupus anticoagulants have an overall incidence of 5%, but within this category, patients with SLE have a 35% increase incidence.
- ▶ Does this mean we anticoagulated all types--no

# Diagnostic Criteria

- ▶ Clinical Criteria
  - ▶ Vascular thrombosis in absence of vasculitis
  - ▶ Or complications associated with pregnancy such as frequent miscarriages, fetal or maternal death.
- ▶ Laboratory Criteria
  - ▶ Lupus anticoagulant assay, IgG or IgM anticardiolipin ab testing or anti-beta-2 glycoprotein 1 ab testing
  - ▶ Diagnosis requires both lab and clinical criteria
  - ▶ Consider testing only in strong histories of unprovoked VTE

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# SUMMARY

- ▶ Surgical Cases—consider risk category of patient with comorbid conditions and weigh risk/benefit of bridging therapy
- ▶ Remember surgical procedures considered at low risk of bleeding (cases that last less than one hour) versus high risk of bleeding
- ▶ Look at dynamic status of patient being consulted-what is their weight, prior surgeries and complications, is their nutritional status stable, is their lifestyle conducive to better outcomes.
- ▶ Medical Cases- as above with identification of life threatening hemorrhage and a “game plan” of how you would reinstitute anticoagulation and/or reversal of a complication of anticoagulants

